REMARKS

Claims 1, 3-4, 6-13, 18, and 20-36 are pending after entry of this paper. Claims 2, 5, 14-17, and 19 have been canceled without prejudice. Applicants reserve the right to prosecute the subject matter of the canceled claims in one or more continuation, continuation-in-part, or divisional applications. Claims 1, 3-4, 6-13, 18, 20-23, 26, 29-36 have been amended. No new matter has been introduced with these amendments. Applicants respectfully request reconsideration in view of the claim amendments and the following remarks.

Response to 35 U.S.C. §112, First Paragraph Rejection

Enablement Rejections: Claims 1 and 3-7

Claims 1 and 3-7 remain rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. Specifically, the Examiner contends that the specification does not enable any person skilled in the art to make or use the invention commensurate in scope with these claims. Applicants respectfully disagree with this rejection.

In order to address the Examiner's rejection and because the Examiner has indicated that the instant specification is enabling for an HSV vector, applicants have amended the claims so that they are directed to an HSV vector. Additionally, claim 1 has been amended to further clarify that the invention is directed to "a transcriptional initiation regulatory region within a human calponin gene comprising a nucleotide sequence shown in Seq. ID No. 1", and a "ICP4 gene".

Because the promoter activity of calponin is the strongest in the region from -260 to +73 and is rapidly reduced in the region from -219 to +73 as shown in Fig. 1A in Yamamura, et al. (*Cancer Res.*, 61, pp. 3969-3977, 2001), applicants assert that the promoter activity is best recognized at the region encompassing 41 nucleotides located at nucleotide positions -260 to -219 in Seq. ID No. 1. This activity is an important property of the cell specific expression replication vector of the instant invention.

As a reminder, the "enablement" requirement of 35 U.S.C. §112 means that a patent specification must describe the claimed invention such that a person skilled in art could make and use the invention. A patent disclosure complies with Section 112 if a person skilled in art can make and use claimed invention without undue experimentation. MPEP §2164.06 states that "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Applicants believe that one skilled in the art would understand how to make and use the invention commensurate in scope with the claims.

For the above reasons applicants believe that one of ordinary skill in the art would conclude that applicants were in possession of the subject matter in claims 1, 3, 4, 6 and 7 at the time the application was filed. Therefore, reconsideration and withdrawal of the rejections under 35 U.S.C. §112, first paragraph, of these claims are respectfully requested.

Enablement Rejections: Claims 26-34

Claims 26-34 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. Specifically, the Examiner contends

that the specification does not enable any person skilled in the art to make or use the invention commensurate in scope with these claims. Applicants respectfully disagree with this rejection.

Claims 26-34 are drawn to therapeutic methods that target proliferating smooth muscle cells. The calponin gene that is used in the instant invention is mainly expressed in smooth muscle cells and thereby allows the targeting of specific types of cancer (see paragraph 87 of the published specification). Claim 26 has been currently amended to further clarify that the claimed therapeutic drug targets proliferating smooth muscle cells. Support for the amendment can be found in paragraphs 1, 31, 32, and 38-40 of the published specification. Claims 27-28 are dependent on claim 26. Claim 29 has been amended to further clarify that the claimed invention is a therapeutic method that targets proliferating myofibroblasts. Support for this amendment can be found in paragraphs 31, 40, and 87 of the published specification. Claim 30 is dependent on claim 29. Claim 31 is directed toward a method of treatment that selectively disrupts proliferating smooth muscle cells in vascular legions. Newly amended claim 32 is directed toward a method of selectively disrupting proliferating glomerulonephritis, *i.e.*, targeting proliferating smooth muscle cells. Support for this amendment can be found in paragraphs 31, 39, 40, and 87 of the published specification. Claims 33 and 34 are dependent on claims 29 through 32.

Applicants assert that the amendments to claims 26-34 have overcome the Examiner's rejection under 35 U.S.C. §112, first paragraph, because they recite methods to treat smooth muscle cell diseases. Therefore, reconsideration and

withdrawal of the rejections under 35 U.S.C. §112, first paragraph, of these claims are respectfully requested.

Response to 35 U.S.C. §112, Second Paragraph Rejection

Claims 10-13

Claims 10-13 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Claims 10-13 have been amended to further clarify the subject matter of the objected phrase "desired protein" by properly depending on claim 9 as suggested by the Examiner. No new subject matter was introduced by these amendments. Applicants respectfully request reconsideration in view of these claim amendments.

Claims 21 and 34

Claims 21 and 34 have been rejected under 35 U.S.C. §112, second paragraph, as being incomplete for omitting essential steps, specifically how the suppression of viral expression/replication is achieved. Applicants respectfully disagree. However, in order to expedite prosecution of the instant application, claims 21 and 34 have been amended to address the Examiner's concerns. Support for these amendments are found in paragraphs 39, 76, and 77 in the published specification. No new subject matter was introduced by these amendments. Applicants respectfully request reconsideration and withdrawal of the §112 rejection to claims 21 and 34 in view of these claim amendments.

Claims 29 and 30

Claims 29 and 30 have been rejected under 35 U.S.C. §112, second paragraph, as being incomplete for omitting essential elements, specifically the proliferating tumor class with disrupted proliferating activity as a result of viral replication inside these cells. Applicants respectfully disagree with the Examiner's contention. However, solely for the purpose of advancing prosecution of the instant application, claim 29 has been amended to address the Examiner's concerns. Support for these amendments may be found in paragraph 36 in the published specification. No new subject matter was introduced by these amendments. The amendment of claim 29 further amends claim 30 because claim 30 is dependent on claim on 29. Applicants respectfully request reconsideration and withdrawal of the §112 rejection in view of these claim amendments.

Claims 29-36

Claims 29-36 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Applicants respectfully disagree with the rejection. However, claims 29-36 have been amended to further clarify the subject matter and address the Examiner's concerns with respect to conforming with U.S. practice. No new subject matter is presented by these amendments. Applicants respectfully request reconsideration in view of these claim amendments.

Claims 35 and 36

Claims 35 and 36 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Applicants respectfully disagree with the Examiner's contention. However, solely in order to further prosecution of the instant application, claim 35 has been amended to further clarify the subject matter and address the Examiner's concerns, for example, with respect to method steps. The amendment is supported by paragraph 15 of the published specification. No new subject matter is presented by this amendment. Claim 36 depends on claim 35 and is thus corrected by the amendment to claim 35. Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C. §112, second paragraph rejections for the above reasons and in view of these claim amendments.

Response to 35 U.S.C. §103(a) Rejections

Martuza et al.

Claims 1 and 3-7 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Martuza et al. (U.S. 5,728,379), in view of Yamamura et al. (*Cancer Res*, May 2001, 61: 3969-3977). Applicants respectfully disagree with this rejection.

There are two approaches for making an oncolytic herpes virus vector that comprises the ICP4 cDNA coupling to a cell-specific promoter and having the ability to proliferate in a specific human malignant tumor. One approach is to delete the thymidine kinase (TK) gene and the other approach is to delete the ribonucleotide

reductase gene. However, the vector that does not have the thymidine kinase gene cannot be expected to be clinically applied because of safety issues.

If vectors still contain the TK gene they are sensitive to ganciclover and acyclovir (see paragraphs 76 and 77 of the published specification). Thus, TK-deleted recombinants can easily be identified and selected by culturing the HSV vectors on medium that contains ganciclover and acyclovir. This method was known at the time that the instant application was filed.

On the other hand, the second method wherein the ICP4 cDNA is coupled to a cell-specific human calponin gene promoter and subjected to homologous recombination at the ribonucleotide reductase gene locus was not known and was not an obvious or easy method to carry out at the time the instant application was filed. Since a gene recombination technique for a herpes virus using a bacterial artificial chromosome (BAC) -based system had not been established at the time when the instant application was filed, a virus clone was separated for the first time by the applicants using a homologous recombination technique and the method described in claim 35. See paragraphs 15-18 of the published specification. Applicants respectfully point out that this second method is more efficient and rapid than the previously known method. By using the ICP4 cDNA the altered vector can be identified because this cDNA expresses a green fluorescent protein that shows fluorescence (see paragraph 17 of the published specification).

Applicants have amended the pending claims which are now drawn to a vector wherein the ribonucleotide reductase gene is deleted thereby allowing separation of the mutants. Martuza et al. (US 5,728,379) alludes to the deletion of the ribonucleotide

reductase gene, however, this concept was not fully comprehended by either Martuza et al. or any other person skilled in the art at the time before the instant application was filed. Applicants enclose herein a copy of a paper authored by Martuza et al. entitled "ONCOLYTIC VIRUSES AS CANCER THERAPEUTICS" dated March 6-13, 2005 to illustrate this point. In this reference Martuza and his colleagues state that they succeeded to produce a ribonucleotide reductase-deleted herpes viral vector comprising ICP4 gene linked to a cell-specific promoter by employing a method for preparing gene recombinants and the "bacterial artificial chromosome (BAC) -based system" which was developed in 2003 by Saeki Y. et al. Therefore, due to the large gap in time, one can only conclude that the second method was not easily manipulated nor was it obvious. Since Martuza et al. were not able to make and use this technique until 2005, applicants argue that one skilled in the art would not have found it obvious to even combine the teachings of Martuza et al. with Yamamura et al. to make the instant invention.

As is understood from FIG. 1 of US 5,728,379, Martuza et al. produced a cell-specific expression replication vector ptkΔL-ALI4 wherein a DNA fragment coupling ICP4, albumin promoter and lacZ is inserted into the thymidine kinase (TK) gene locus by homologous recombination (i.e., tumor cell-specific proliferation due to TK ablation; liver tumor cell-specific proliferation due to ICP4 expression by albumin promoter). Martuza et al., however, did not succeed in producing a cell-specific expression replication vector where a DNA fragment coupling ICP4, albumin promoter and lacZ is inserted into the ribonucleotide reductase (ICP6) gene locus by homologous recombination. Martuza et al. produced only the replicable HSV-1 vector G207 which

lacks copies of the γ34.5 (ICP34.5) gene involved in replication in neural cells and in which only LacZ gene is inserted in the ribonucleotide reductase (ICP6) gene locus (tumor cell-specific proliferation due to TK ablation; non cell-specific due to lack of ICP4 gene coupling to a cell-specific promoter). It took Martuza et al. 10 years (from 1995 to 2005) to produce a herpes viral vector ablating the ribonucleotide reductase gene and comprising a ICP4 gene coupled to a cell-specific promoter. Thus, applicants argue that it was difficult to produce such a viral vector even by one skilled in the art at the time that the instant application was filed.

Applicants further reason that Martuza et al. and others skilled in the art were unable to make such a construct because any one of lacZ, a cell-specific promoter, and an ICP4 gene may ablate when attempting to construct a herpes viral vector wherein a DNA fragment comprising lacZ and an ICP4 gene coupled to a cell-specific promoter is inserted into the ribonucleotide reductase (ICP6) gene locus by homologous recombination, or because of the difficulty of cloning a vector even when such a vector with appropriate recombination of the above three has been produced.

Applicants were able to purify a single clone of a recombinant virus vector d12.CALP△RR by the steps comprising: (i) appropriately positioning a marker gene (lacZ) which is expressed by a promoter of ICP6 gene when correctly inserted into the ICP6 gene locus, and positioning ICP4 gene and a marker gene (EGFP) in order to confirm that the operator was located downstream of the calponin promoter; (ii) constructing a vector by homologous recombination; (iii) selecting, by a limiting dilution, a clone in which calponin promoter effectively operates by IRES-mediated expression of EGFP, with the use of the ICP4(-) SK-LMS-1 human smooth muscle tumor cells that are

calponin-expressing cells; and (iv) selecting a ribonucleotide reductase-deleted clone by the ribonucleotide reductase promoter-mediated lacZ expression, with the use of ICP4(+) VeroE5 cells. Hence, applicants submit that it was not easy even for a skilled artisan to produce a ribonucleotide reductase-deleted herpes virus vector comprising an ICP4 gene coupled to a calponin promoter. For the above reasons, applicants argue that it was not obvious in 2002 to combine the above references to result in the claimed invention nor to make and use the instant invention.

Reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a) of the claims 1, 3, 4, 6 and 7 are respectfully requested for the above reasons.

Chung et al. in view of Yamamura et al.

Claims 1, 3-7, 14, 16-20, and 25-28 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Chung et al. (J. Virol., 1999, 73: 7556-7564), in view of Yamamura et al. (*Cancer Res*, May 2001, 61: 3969-3977). Applicants respectfully disagree with this rejection.

Claim 1 has been amended to incorporate claim 15 which contains presumably acceptable subject matter because it has not been previously rejected. Claim 1 has also been amended to further clarify that the claim is drawn to an "ICP4 gene" instead of a "predetermined gene."

Chung describes a predetermined viral gene γ34.5. Chung describes the use of one promoter, the B-*myb* promoter, which controls the HSV-mutant. Chung states that the B-*myb* promoter is regulated in a "tight fashion" thus restricting the expression of the γ34.5 gene (see Chung et al., page 7562, right column). Similarly Yamamura utilizes

only one promoter to drive the expression of the ICP4 gene (see Yamamura et al., page 3974, left column). Both of these references teach away from using multiple promoters. Yamamura states one of the main problems with using viral vectors for treating disease is the side effects of the non-specific effects that can occur. (*Id.*, page 3974, right column). Yamamura states that using one promoter has been commonly utilized in order to achieve an efficient vector for the treatment of cancer. (*Id.*) These references teach that the vectors should be tightly regulated in order to effectively treat the targeted cancer cells. Alternatively, the instant invention uses two promoters, the calponin promoter and the ICP4 gene promoter, in order to achieve a HSV vector that targets proliferating smooth muscle cells. Therefore, the combination of Chung and Yamamura does not teach or suggest the instant invention as claimed.

Reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a) of the claims 1, 3, 4, 6, 7, 18, 20, and 25-28 are respectfully requested for the above reasons.

Van Meir et al.

Claims 1, 3-18, 20-22, and 25-28 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Van Meir et al. (PGPUB 2005/0074430), in view of both LaFace (U.S. 6,649,158) and Yamamura et al. Applicants respectfully disagree with this rejection.

Claim 1 has been amended to incorporate claim 19 which contains presumably acceptable subject matter because it has not been previously rejected. This claim has also been amended to further clarify that the claim is drawn to a method comprising "inserting a DNA fragment comprising the transcriptional initiation regulatory region of

the human calponin gene into a ribonucleotide reductase gene locus by a homologous recombination." Van Meir allegedly teaches the instant invention except for the calponin promoter and the 4F2 enhancer as taught by Yamamura. The Examiner further combines LaFace for allegedly teaching that expression vectors can induce expression of therapeutic proteins. However, none of the references either alone or in combination teach or suggest the invention as presently claimed. Because this combination of Van Meir, LaFace, and Yamamura does not teach this insertion method step that has been added, applicants respectfully assert that the instantly claimed invention is not obvious over the cited art.

Reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a) of the claims 1, 3, 4, 6-13, 18, 20-22, and 25-28 are respectfully requested for the above reasons.

Chung et al. taken with Yamamura et al. in view of Tjuvajev et al.

Claims 1, 3-7, 14, 16-20, and 23-28 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Chung et al. (J. Virol., 1999, 73: 7556-7564), taken with Yamamura et al. (*Cancer Res*, May 2001, 61: 3969-3977), as applied to claims 3-7, 14, 16-20, and 25-28, in further view of Tjuvajev et al. (*Cancer Res*, 1998, 58: 4333-4341, Abstract). Applicants respectfully disagree with this rejection.

Claim 1 has been amended to incorporate claim 15 which contains presumably acceptable subject matter because it has not been previously rejected. Claim 1 has also been amended to further clarify that the claim is drawn to an "ICP4 gene" instead of a "predetermined gene."

Reconsideration and withdrawal of the rejections under 35 U.S.C. §103(a) of the claims 1, 3, 4, 6, 7, 18, 20, and 23-28 are respectfully requested for the above reasons.

Double Patenting Rejection

Claims 1, 3, 4, 6 and 7 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of co-pending Application No. 10/477,797. Since the conflicting claims have not in fact been patented, this is a provisional obviousness-type double patenting rejection.

In response, applicants again respectfully request that the provisional double-patenting rejection be held in abeyance due to the provisional nature of the rejection until one of the applications is allowed. Upon notice of otherwise allowable subject matter, applicants will address the rejection. Applicants note that it is proper when dealing with otherwise allowable subject matter in co-pending applications to withdraw a provisional rejection in the most advanced application, allow it to issue, and make a (non-provisional) rejection in the remaining application.

CONCLUSION

Thus, applicants respectfully submit that the invention as recited in the claims as presented herein is allowable over the art of record, and respectfully request that the respective rejections and objections be withdrawn.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **13-4500**, Order No. 4439-4022.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **13-4500**, Order No. 4439-4022.

Respectfully submitted,
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